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(12) # EUROPEAN PATENT SPECIFICATION

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(54) **Crystalline 4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium trihydrate, process therefor and compositions and use thereof.**

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Description

This invention relates to crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate and a process therefor, where the end product is obtained in particularly pure form and at high yields in a one-pot procedure, and compositions containing said salt and its use in their manufacture.

GB-A-2166741 discloses the preparation of 4-amino-1-hydroxybutylidene-1,1-diphosphonic acid and described its potentiometric titration in solution. EP-A-0039033 discloses a process for the preparation of omega amino-1-hydroxyalkylidene-1-bisphosphonic acids but did not describe any salt of 4-amino-1-hydroxybutylidene-1,1-diphosphonic acid. Analytical methods for the determination of 4-amino-1-hydroxybutylidene-1,1-diphospohonic acid monosodium salt were described before 9 June 1989.

It is known according to U.S. Patent 4,407,761 to prepare 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid by reacting an aminocarboxylic acid with a phosphonating reactant and then hydrolyzing the reaction mixture by addition of concentrated hydrochloric acid with heating. Problems result from this reaction whereby it does not remain homogeneous and local solidification occurs. This solidification causes variable yields, which in part results from the exothermic nature of the reactions with development of hot spots.

Our new process allows the reaction to remain fluid and homogeneous and makes manufacturing of crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate possible. It also has the advantage of requiring only one process step and provides a yield of 85-90%.

It has been found that pure crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate can surprisingly be obtained (in high yields) by the reaction of 4-aminobutyric acid with phosphonating reactants in the presence of methanesulfonic acid at a temperature of less than 85 °C to yield a reaction mixture containing 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid; the crystalline monosodium salt trihydrate is crystallized directly from the reaction mixture in about 90% yield after quenching, hydrolysis, and pH adjustment to about 4.3 with no further purification necessary.

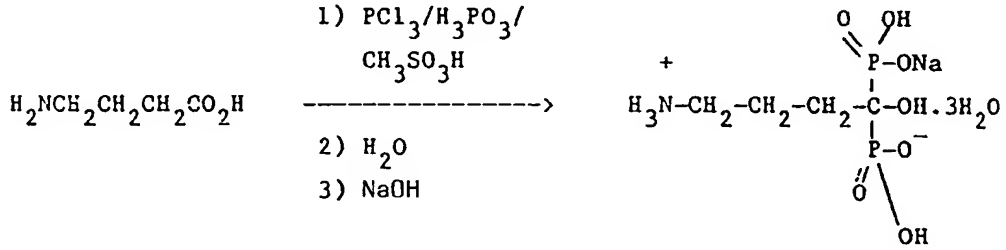
The phosphonylation reaction generally takes place at temperatures of about 65 °C.

Preferably 1 to 2, particularly 1.5 moles of H_3PO_3 and 1 to 2.5, particularly 2.4 mols of PCl_3 are used per mol of aminobutyric acid.

It is not necessary to use a diluent when methanesulfonic acid is used in the reaction.

In general, the hydrolysis is completed after about 3 hours boiling under reflux, as is shown by the chromatographic test of the reaction solution.

The reaction is schematically represented as follows:



$C_4H_9NO_2$

MW 103.12

$C_4H_{12}NNaO_7P_2 \cdot 3H_2O$

MW 325.13

Crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate described here is useful as a pharmaceutical composition and for the treatment or prevention of diseases involving bone resorption. Such diseases as hypercalcemia of malignancy, Paget's disease, and osteoporosis are advantageously treated with crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate made according to the process of the present invention.

The following examples are illustrative of the practice of the invention without being limiting in any way.

EXAMPLE 1

Preparation of crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydate

A 250 mL flask was fitted with a mechanical stirrer, a thermcouple, an addition funnel and a reflux condenser through which is circulated -20 °C brine. The system was connected to a caustic scrubber which places a back pressure of (4.8 - 6.9)10^4 Pa (7-10psi) on the system. The system was flushed with nitrogen and charged with 20 g (0.19 mol) of aminobutyric acid, 80 mL of methanesulfonic acid, and 24 g (0.29 mol) of phosphorous acid. For larger scale operations, the methanesulfonic acid can be charged first, followed by the 4-aminobutyric acid and phosphorus acid. Upon mixing, the heat of neutralization and solution increased the reaction temperature to 75 °C. The suspension was aged for 15 minutes at 70-75 °C resulting in a clear colorless solution. The solution was cooled to 35 °C and phosphorus trichloride (PCl_3), 40 mL (0.46 mol) was added cautiously over 20 minutes. The reaction was then heated to 65 °C and aged at that temperature for 20 hours. The reaction should not be allowed to get much above 65 °C. The reaction becomes self-heating above 85 °C and under adiabatic conditions the temperature will increase steadily. At about 150 degrees an exotherm accompanied by a large pressure release occurs. It is therefore recommended that the reaction be immediately quenched into cold water if the temperature reaches 85 °C. The reaction was then cooled to 25 °C and added to 200 mL of deionized water over 5 minutes. The flask was rinsed with an additional 100 mL of water and the combined solution aged at 95-100 °C for 5 hours. The reaction was cooled to 20 °C and maintained at 20-25 °C while the pH was adjusted to 4.3 with ca. 80 mL of 50% NaOH. The resulting white suspension was then cooled to 0-5 °C and aged for 1 hour. The pH was readjusted to 4.3 if necessary and the suspension aged at 0-5 °C for an additional 2 hours. The product was collected by filtration, then washed with 2 x 50 mL of cold (0-5 °C) water and 100 mL of 95% EtOH. The yield after air drying at 40 °C to constant weight was 56.4 g (90%).

EXAMPLE 2

Analysis of crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate

The reaction product of Example 1 was analysed with the results as follows:-

Tests	Results
color,form,appearance	fine white free flowing crystalline powder
Particle size	10-100 μ, average <50
Melting point	inserted at 245, starts to melt at 257, decomposes at 262.5
Assay (NaOH titration)	99.7%
Assay (complexometric tritration)	99.9%
HPLC	99.5%
Karl Fisher	16.6% (theory 16.6%)
Loss on drying	16.7%
GC-residual ethanol	<0.01%
TLC for other acids	<0.01% (not detected)
Heavy metals	<20 ppm
pH of 0.5% H_2O solution	4.36
IR	conforms
X-ray	conforms
Flame test for Na	conforms

Microchemical analysis		
	Theory	Found
Carbon	14.77	14.67
Hydrogen	5.54	5.58
Nitrogen	4.31	4.22
Sodium*	7.08	7.00
Phosphorous	19.08	19.00
Residual chloride		<0.05

*Determined by AA.

Claims

Claims for the following Contracting States : AT, BE, DK, FR, DE, GB, NL, IT, LU, CH, LI, SE

1. Crystalline 4-amino-1-hydroxybutylidine-1,1-bisphosphonic acid monosodium salt trihydrate.

2. The compound according to claim 1 in the form of a free flowing powder.

3. A compound according to claim 1 or claim 2 for use in the manufacture of a pharmaceutical composition.

4. A pharmaceutical composition comprising a compound according to claim 1 or claim 2.

5. A process for the preparation of a compound according to claim 1 or claim 2 which comprises:
   (a) reacting 4-aminobutyric acid with a mixture of phosphorous acid and PCl_3 in the presence of methanesulphonic acid at a temperature of less than 85 °C;
   (b) treating with water,
   (c) bringing the pH to 4.3 with sodium hydroxide solution at a temperature of 20-25 °C,
   (d) cooling to 0-5 °C and
   (e) collecting the desired compound by filtration, washing with water and 95% ethanol and air drying.

6. A process according to claim 5 wherein step (a) is performed in the absence of a diluent.

7. A process according to claim 5 or claim 6 wherein step (a) is performed at about 65 °C and step (e) at 40 °C.

8. A process according to any of claims 5 to 7 wherein 1.5 moles of H_3PO_3 and 2.4 moles of PCl_3 are used per mol of 4-aminobutyric acid.

9. A process according to any of claims 5 to 8 wherein step (c) employs 50% sodium hydroxide solution.

10. A process according to any of claims 5 to 9 wherein the solution obtained in stage (b) is aged at 95-100 °C prior to commencement of step (c).

Claims for the following Contracting States : GR, ES

1. A process for the preparation of crystalline 4-amino-1-hydroxybutylidine-1,1-bisphosphonic acid monosodium salt trihydrate which comprises:
   (a) reacting 4-aminobutyric acid with a mixture of phosphorous acid and PCl_3 in the presence of methanesulphonic acid at a temperature of less than 85 °C;
   (b) treating with water,
   (c) bringing the pH to 4.3 with sodium hydroxide solution at a temperature of 20-25 °C,
   (d) cooling to 0-5 °C and
   (e) collecting the desired compound by filtration, washing with water and 95% ethanol and air drying.

2. A process according to claim 1 wherein step (e) is performed at 40 °C and the product is in the form of a free flowing powder.

3. A process according to claims 1 or 2 wherein step (a) is performed in the absence of a diluent.

4. A process according to claims 1 to 3 wherein step (a) is performed at about 65 °C.

5. A process according to any of claims 1 to 4 wherein 1.5 moles of H_3PO_3 and 2.4 moles of PCl_3 are used per mol of 4-aminobutyric acid.

6. A process according to any of claims 1 to 5 wherein step (c) employs 50% sodium hydroxide solution.

7. A process according to any of claims 1 to 6 wherein the solution obtained in stage (b) is aged at 95-100 °C prior to commencement of step (c).

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, DK, FR, DE, GB, NL, IT, LU, CH, LI, SE

1. Kristallines 4-Amino-1-hydroxybutylidin-1,1-bisphosphonsäure-Mononatriumsalz-Trihydrat.

2. Die Verbindung nach Anspruch 1 in Form eines freifließenden Pulvers.

3. Eine Verbindung nach Anspruch 1 oder Anspruch 2 zur Verwendung bei der Herstellung einer pharmazeutischen Zusammensetzung.

4. Eine pharmazeutische Zusammensetzung, umfassend eine Verbindung nach Anspruch 1 oder Anspruch 2.

5. Ein Verfahren zur Herstellung einer Verbindung nach Anspruch 1 oder Anspruch 2, das umfaßt:
   (a) Umsetzen von 4-Aminobuttersäure mit einer Mischung aus phosphoriger Säure und PCl_3 in Gegenwart von Methansulfonsäure bei einer Temperatur von Weniger als 85 °C,
   (b) Behandeln mit Wasser,
   (c) den pH-Wert mit Natriumhydroxidlösung bei einer Temperatur von 20-25 °C auf 4,3 zu bringen,
   (d) Abkühlen auf 0-5 °C, und
   (e) Sammeln der erwünschten Verbindung durch Filtration, Waschen mit Wasser und 95%igem Ethanol und Lufttrocknen.

6. Ein Verfahren nach Anspruch 5, worin Schritt (a) in Abwesenheit eines Verdünnungsmittels durchgeführt wird.

7. Ein Verfahren nach Anspruch 5 oder Anspruch 6, worin Schritt (a) bei etwa 65 °C und Schritt (e) bei 40 °C durchgeführt wird.

8. Ein Verfahren nach irgendeinem der Ansprüche 5 bis 7, worin 1,5 Mol H_3PO_3 und 2,4 Mol PCl_3 pro Mol 4-Aminobuttersäure verwendet werden.

9. Ein Verfahren nach irgendeinem der Ansprüche 5 bis 8, worin Schritt (c) eine 50%ige Natriumhydroxidlösung verwendet.

10. Ein Verfahren nach irgendeinem der Ansprüche 5 bis 9, worin die in Stufe (b) erhaltene Lösung vor Beginn des Schrittes (c) bei 95-100 °C gealtert wird.

Patentansprüche für folgende Vertragsstaaten : GR, ES

1. Ein Verfahren zur Herstellung von kristallinem 4-Amino-1-hydroxybutylidin-1,1-bisphosphonsäure-Mononatriumsalz-Trihydrat, das umfaßt:
   (a) Umsetzen von 4-Aminobuttersäure mit einer Mischung aus phosphoriger Säure und PCl_3 in Gegenwart von Methansulfonsäure bei einer Temperatur von weniger als 85 °C,

(b) Behandeln mit Wasser,
(c) den pH-Wert mit Natriumhydroxidlösung bei einer Temperatur von 20-25 °C auf 4,3 zu bringen,
(d) Abkühlen auf 0-5 °C, und
(e) Sammeln der erwünschten Verbindung durch Filtration, Waschen mit Wasser und 95%igem Ethanol und Lufttrocknen.

2. Ein Verfahren nach Anspruch 1, worin Schritt (e) bei 40 °C durchgeführt wird, und das Produkt in Form eines freifließenden Pulvers vorliegt.

3. Ein Verfahren nach Anspruch 1 oder 2, worin Schritt (a) in Abwesenheit eines Verdünnungsmittels durchgeführt wird.

4. Ein Verfahren nach den Ansprüchen 1 bis 3, worin Schritt (a) bei etwa 65 °C durchgeführt wird.

5. Ein Verfahren nach irgendeinem der Ansprüche 1 bis 4, worin 1,5 Mol H_3PO_3 und 2,4 Mol PCl_3 pro Mol 4-Aminobuttersäure verwendet werden.

6. Ein Verfahren nach irgendeinem der Ansprüche 1 bis 5, worin Schritt (c) eine 50%ige Natriumhydroxidlösung verwendet.

7. Ein Verfahren nach irgendeinem der Ansprüche 1 bis 6, worin die in Stufe (b) erhaltene Lösung vor Beginn des Schrittes (c) bei 95-100 °C gealtert wird.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, DK, FR, DE, GB, NL, IT, LU, CH, LI, SE

1. Trihydrate cristallin du sel monosodique de l'acide 4-amino-1-hydroxybutylidène-1,1-bisphosphonique.

2. Composé selon la revendication 1, sous la forme d'une poudre s'écoulant librement.

3. Composé selon la revendication 1 ou 2, destiné à être employé pour la fabrication d'une composition pharmaceutique.

4. Composition pharmaceutique, comprenant un composé selon la revendication 1 ou 2.

5. Procédé de préparation d'un compose selon la revendication 1 ou 2, selon lequel :
(a) on fait réagir de l'acide 4-aminobutyrique avec un mélange d'acide phosphoreux et de PCl_3, en présence d'acide méthanesulfonique, à une température inférieure à 85 °C ;
(b) on traite avec de l'eau ;
(c) on ajuste le pH à 4,3 avec une solution d'hydroxyde de sodium à une température de 20 à 25 °C ;
(d) on refroidit jusqu'à 0-5 °C, et
(e) on récupère le composé requis par filtration, on le lave avec de l'eau et de l'éthanol à 95 % et on le sèche à l'air.

6. Procédé selon la revendication 5, dans lequel l'étape (a) est effectuée en l'absence d'un diluant.

7. Procédé selon la revendication 5 ou 6, dans lequel l'étape (a) est effectuée à environ 65 °C, et l'étape (e) à 40 °C.

8. Procédé selon l'une quelconque des revendications 5 à 7, dans lequel on emploie 1,5 moles de H_3PO_3 et 2,4 moles de PCl_3 par mole d'acide 4-aminobutyrique.

9. Procédé selon l'une quelconque des revendications 5 à 8, dans lequel, dans l'étape (c), on utilise une solution à 50 % d'hydroxyde de sodium.

10. Procédé selon l'une quelconque des revendications 5 à 9, dans lequel la solution obtenue dans l'étape (b) est vieillie à 95-100 °C avant le début de l'étape (c).

Revendications pour les Etats contractants suivants : GR, ES

1. Procédé de préparation du trihydrate cristallin du sel monosodique de l'acide 4-amino-1-hydroxybutylidène-1,1-bisphosphonique, selon lequel :
   (a) on fait réagir de l'acide 4-aminobutyrique avec un mélange d'acide phosphoreux et de PCl_3, en présence d'acide méthanesulfonique, à une température inférieure à 85 °C ;
   (b) on traite avec de l'eau ;
   (c) on ajuste le pH à 4,3 avec une solution d'hydroxyde de sodium à une température de 20 à 25 °C ;
   (d) on refroidit jusqu'à 0-5 °C, et
   (e) on récupère le composé requis par filtration, on le lave avec de l'eau et de l'éthanol à 95 % et on le sèche à l'air.

2. Procédé selon la revendication 1, dans lequel l'étape (e) est effectuée à 40 °C, et le produit est sous la forme d'une poudre s'écoulant librement.

3. Procédé selon la revendication 1 ou 2, dans lequel l'étape (a) est effectuée en l'absence d'un diluant.

4. Procédé selon les revendications 1 à 3, dans lequel l'étape (a) est effectuée à environ 65 °C.

5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel on emploie 1,5 moles de H_3PO_3 et 2,4 moles de PCl_3 par mole d'acide 4-aminobutyrique.

6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel, dans l'étape (c), on utilise une solution à 50 % d'hydroxyde de sodium.

7. Procédé selon l'une quelconque des revendications 1 à 6, dans lequel la solution obtenue dans l'étape (b) est vieillie à 95-100 °C avant de commencer l'étape (c).